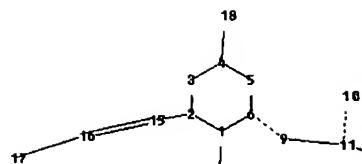
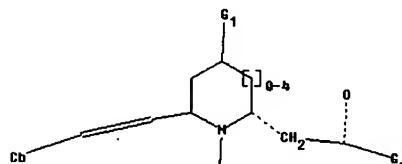


10/813,647

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\* \* \* \* \* \* \* \* \* \* \* \* \* STN Columbus \* \* \* \* \* \* \* \* \* \* \* \* \* \* \* \* \*

FILE 'HOME' ENTERED AT 09:19:43 ON 10 OCT 2006

=> file reg  
=>Uploading C:\Program Files\Stnexp\Queries\10813647b.str



chain nodes :

9 10 11 13 15 16 17 18 20

ring nodes :

1 2 3 4 5 6

chain bonds :

1-20 2-15 4-18 6-9 9-11 10-11 11-13 15-16 16-17

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6

exact/norm bonds :

1-2 1-6 1-20 2-3 3-4 4-5 4-18 5-6 6-9 10-11 11-13

exact bonds :

2-15 9-11 15-16 16-17

isolated ring systems :

containing 1 :

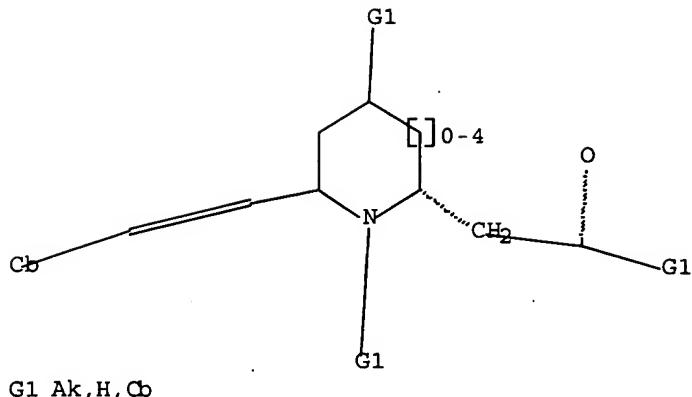
G1:Ak,H,Cb

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 9:CLASS 10:CLASS 11:CLASS  
13:CLASS 15:CLASS 16:CLASS 17:Atom 18:CLASS 20:CLASS

L1 STRUCTURE UPLOADED

=> dis 11  
L1 HAS NO ANSWERS  
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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L2          1 SEA SSS SAM L1

=> s l1 full
L3          9 SEA SSS FUL L1

=> file caplus
=> s L3
L4          4 L3

=> s l4 and pd<july 1999
    19884408 PD<JULY 1999
    (PD<19990700)
L5          1 L4 AND PD<JULY 1999

=> dis bib abs hitstr

L5  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
AN  1999:510839  CAPLUS Full-text
DN  131:281005
TI  Lobeline: Structure-Affinity Investigation of Nicotinic Acetylcholinergic
    Receptor Binding
AU  Flammia, Dwight; Dukat, Malgorzata; Damaj, M. Imad; Martin, Billy;
    Glennon, Richard A.
CS  Department of Medicinal Chemistry School of Pharmacy and Department of
    Pharmacology and Toxicology School of Medicine, Virginia Commonwealth
    University, Richmond, VA, 23298-0540, USA
SO  Journal of Medicinal Chemistry (1999), 42(18), 3726-3731
    CODEN: JMCMAR; ISSN: 0022-2623
PB  American Chemical Society
DT  Journal
LA  English
AB  (-)Lobeline (1) and (-)nicotine (2) bind at neuronal nicotinic cholinergic
    (nACh) receptors with high affinity ( $K_i = 4$  and  $2$  nM, resp.). Previous
    attempts to determine whether lobeline fits the currently accepted nicotinic
    pharmacophore model have led to suggestions that the carbonyl function, rather
    than the hydroxyl group, is a major contributor to binding. Interestingly,
    however, it has never been empirically demonstrated that either oxygen
    function is actually required for interaction with the receptor. In the
```

present investigation we systematically examined a number of abbreviated analogs of lobeline and found that removal of either one or both oxygen functions reduces the affinity of lobeline by at least 25-fold; furthermore, oxidation of the (-)lobeline hydroxyl group (to afford lobelanine) or reduction of the carbonyl group (to afford lobelanidine) also resulted in decreased affinity. Although it is likely that both oxygen functions contribute to the high affinity of (-)lobeline at nACh receptors, it is concluded that the presence of both oxygen functions is not a requirement for binding; i.e., replacement of the (-)lobeline hydroxyl group with a chloro group had no effect on affinity. Another finding of the present investigation is that removal of either one or both oxygen functions of lobeline results in compds. that retain the analgesic activity and potency of (-)lobeline, indicating that there is no direct relationship between neuronal nicotinic cholinergic (primarily  $\alpha_4\beta_2$  type) receptor affinity and spinal analgesia as measured in the tail-flick assay.

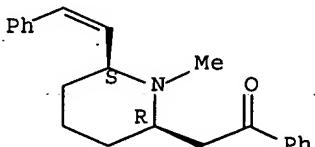
IT 246178-16-5P 246178-17-6P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (lobeline analogs: structure-affinity investigation of neuronal nicotinic receptor binding)

RN 246178-16-5 CAPLUS

CN Ethanone, 2-[(2R,6S)-1-methyl-6-(2-phenylethenyl)-2-piperidinyl]-1-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

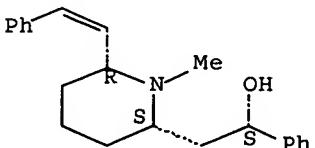


RN 246178-17-6 CAPLUS

CN 2-Piperidineethanol, 1-methyl- $\alpha$ -phenyl-6-(2-phenylethenyl)-, (2S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

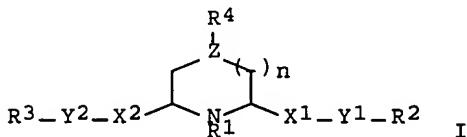
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L6 3 L4 NOT L5

=> dis 16 1-3 bib abs

L6 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2005:2187 CAPLUS Full-text  
 DN 142:93692  
 TI Preparation of 2,6-disubstituted piperidines and piperazines for the treatment of CNS diseases  
 IN Crooks, Peter A.; Dwoskin, Linda; Jones, Marlon D.; Miller, Dennis Keith; Norholm, Seth Davin; Zheng, Guangrong; Krishamurthy, Sairam  
 PA USA  
 SO U.S. Pat. Appl. Publ., 27 pp., Cont.-in-part of U.S. Ser. No. 231,156.  
 CODEN: USXXCO  
 DT Patent  
 LA English  
 FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004266824 US 6455543 US 2003100547 US 6943177	A1 B1 A1 B2	20041230 20020924 20030529 20050913	US 2004-813647 US 2000-628557 US 2002-231156	20040331 20000728 20020830
PRAI	US 1999-146144P US 2000-628557 US 2002-231156	P A3 A2	19990730 20000728 20020830		
OS	MARPAT				
GI					



AB Title compds. represented by the formula I [wherein X1 = CH2; Y1 = CHO or C=O; X2-Y2 = cis/trans-carbon-carbon double bond; Z = CH; R1, R4 = independently H or alkyl; R2, R3 = independently (un)saturated hydrocarbon ring or (un)substituted benzene; n = 0-3; and pharmaceutically effective salts thereof, including resolved diastereomers, enantiomers thereof] were prepared. For example, lobelanidine was stirred overnight in 85% H3PO4 at 60° to give 78.6% cis-2,6-di-trans-styrylpiperidine. I showed activity in [3H]nicotine binding assay, [3H]MLA binding assay, inhibition of nicotine-evoked 86Rb+ efflux assay, and etc. Thus, I are useful to treat diseases of the central nervous system, drug abuse, and withdrawal therefrom as well as treating eating disorders (no data).

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2004:723970 CAPLUS Full-text  
 DN 141:271405  
 TI Lobeline analogs with enhanced affinity and selectivity for plasmalemma and vesicular monoamine transporters  
 AU Miller, Dennis K.; Crooks, Peter A.; Zheng, Guangrong; Grinevich, Vladimir P.; Norholm, Seth D.; Dwoskin, Linda P.  
 CS College of Pharmacy, University of Kentucky, Lexington, KY, USA  
 SO Journal of Pharmacology and Experimental Therapeutics (2004), 310(3), 1035-1045

CODEN: JPETAB; ISSN: 0022-3565

PB American Society for Pharmacology and Experimental Therapeutics  
 DT Journal  
 LA English

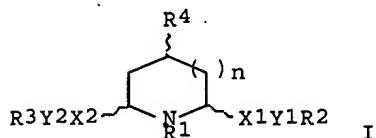
AB Lobeline attenuates the behavioral effects of psychostimulants in rodents and inhibits the function of nicotinic receptors (nAChRs), dopamine transporters (DATs), and vesicular monoamine transporters (VMAT2s). Monoamine transporters are considered valid targets for drug development for the treatment of methamphetamine abuse. In the current study, a series of lobeline analogs were evaluated for affinity and selectivity at these targets. None of the analogs was more potent than nicotine at the [<sup>3</sup>H]methyllycaconitine binding site ( $\alpha 7^*$  nAChR subtype). Lobeline tosylate was equipotent with lobeline in inhibiting [<sup>3</sup>H]nicotine binding but 70-fold more potent in inhibiting nicotine-evoked <sup>86</sup>Rb<sup>+</sup> efflux, demonstrating antagonism of  $\alpha 4\beta 2^*$  nAChRs. Compared with lobeline, the defunctionalized analogs lobelane, mesotransdiene, and (-)-trans-transdiene showed dramatically reduced affinity at  $\alpha 4\beta 2^*$  nAChRs and a 15- to 100-fold higher affinity ( $K_i$  = 1.95, 0.58, and 0.26  $\mu$ M, resp.) at DATs. Mesotransdiene and (-)-trans-transdiene competitively inhibited DAT function, whereas lobelane and lobeline acted noncompetitively. 10S/10R-MEPP [*N*-methyl-2R-(2R/2S-hydroxy-2-phenylethyl)-6S-(2-phenylethyl)piperidine] and 10R-MESP [*N*-methyl-2R-(2R-hydroxy-2-phenylethyl)-6S-(2-phenylethen-1-yl)piperidine] were 2 to 3 orders of magnitude more potent ( $K_i$  = 0.01 and 0.04  $\mu$ M, resp.) than lobeline in inhibiting [<sup>3</sup>H]serotonin uptake; 10S/10R-MEPP showed a 600-fold selectivity for this transporter. Uptake results using hDATs and human serotonin transporters expressed in human embryonic kidney-293 cells were consistent with native transporter assays. Lobelane and ketoalkene were 5-fold more potent ( $K_i$  = 0.92 and 1.35  $\mu$ M, resp.) than lobeline ( $K_i$  = 5.46  $\mu$ M) in inhibiting [<sup>3</sup>H]methoxytetrabenazine binding to VMAT2 in vesicle preps. Thus, structural modification (defunctionalization) of the lobeline mol. markedly decreases affinity for  $\alpha 4\beta 2^*$  and  $\alpha 7^*$  nAChRs while increasing affinity for neurotransmitter transporters, affording analogs with enhanced selectivity for these transporters and providing new leads for the treatment of psychostimulant abuse.

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2001:100973 CAPLUS Full-text  
 DN 134:147501  
 TI Preparation of cis-2,6-disubstituted piperidines for the treatment of psychostimulant abuse and withdrawal, eating disorders, and central nervous system diseases and pathologies.  
 IN Dwoskin, Linda P.; Crooks, Peter A.; Jones, Marlon D.  
 PA University of Kentucky Research Foundation, USA  
 SO PCT Int. Appl., 28 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001008678	A1	20010208	WO 2000-US20553	20000728
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,			

CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
AU 2000063867 A5 20010219 AU 2000-63867 20000728  
EP 1513513 A1 20050316 EP 2000-950822 20000728  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, FI, CY  
PRAI US 1999-146144P P 19990730  
WO 2000-US20553 W 20000728  
OS MARPAT 134:147501  
GI



AB A method for treatment of drug dependence, drug withdrawal, an eating disorder, or a CNS disease or pathol. comprises administration of title compds. [I; n = 0-3; X1Y1, X2Y2 = C-C single, double, or triple bond, C-S bond, C-Se bond, C-O bond, (N-alkyl) C-N single or double bond, N-N double bond; R1, R4 = H, alkyl; R1R4 = atoms to form a ring including CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>, (CH<sub>2</sub>)<sub>3</sub>, cis-CH:CH, cis-CH<sub>2</sub>CH:CH; R2, R3 = (unsatd.) hydrocarbon ring, N-, O-, S-, and/or Se-containing heterocycl, o-, m-, or p-substituted benzene; with provisos]. Thus, lobelanidine was stirred overnight in 85% H<sub>3</sub>PO<sub>4</sub> at 60° to give 78.6% cis-2,6-di-trans-styrylpiperidine. Tested I showed K<sub>i</sub> = 0.0043 μM to ≥100 μM in the high affinity [<sup>3</sup>H] nicotine binding assay.

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> log Y			
COST IN U.S. DOLLARS	SINCE FILE	TOTAL	
	ENTRY	SESSION	
FULL ESTIMATED COST	15.74	182.89	
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL	
CA SUBSCRIBER PRICE	ENTRY	SESSION	
	-3.00	-3.00	

STN INTERNATIONAL LOGOFF AT 09:21:17 ON 10 OCT 2006